SETBP1 Genetics: Bite-Sized Breakthroughs

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Genetic architecture of childhood speech disorder: a review

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About the Author:
Welcome to our first "SETBP1 Genetics: Bite-sized Breakthrough", featuring a review article published by Dr. Angela Morgan at Murdoch Children's Research Institute (MCRI) in Melbourne, VIC, Australia! If you are new to our community, Dr. Morgan has worked closely with our families since 2019, collaborating over the years with several specialists and researchers well-known in the SETBP1 community, including Dr. Brejge van Bon, Dr. Simon E Fisher, Dr. Sid, and Maggie Wong. Her previous 2021 publication revealed a striking speech presentation within SETBP1-HD individuals that implicated both motor (childhood apraxia of speech; CAS) and language (phonological errors) systems and expanded the known phenotype for SETBP1-HD.

Background:
A genetic basis for speech disorders has been suspected since the early 1950s, however, the molecular basis has remained unknown for many decades. Aside from *FOXP2* in 2001, the link between CAS and specific genes and their variants has eluded scientists. Thanks to advances in genomic sequencing technology and improved analytics, researchers have identified monogenic (single-gene) bases for CAS that may underlie speech delay and language impairment such as stuttering or phonological disorder, with varying levels of evidence and support. Interestingly, the majority of these new candidate genes are previously associated with neurodevelopmental conditions spanning intellectual disability, autism, and epilepsy therefore broadening the scientific community's understanding of a potential dual role of genes in development and speech function. This review sheds light on these new findings, using data from three different previously published patient cohorts.

Main Findings:
Most candidate genes identified across all three cohorts code for a protein involved in chromatin modification or transcriptional regulation, some of which are transcription factors (such as SETBP1). Importantly, these candidate genes are highly co-expressed in the human embryonic brain, in regions known to subserve speech function. This review provides the first evidence that CAS could be a neurodevelopmental disorder due to the abnormal expression of genes in white-matter tracts of the brain that are critical for speech development. We, as a field, know that SETBP1 expression is highest in embryonic stages before birth, and this study suggests future research investigating early SETBP1 expression in development could benefit our understanding of SETBP1-HD not just for the neurodevelopmental but also speech phenotypes seen in affected individuals.

What does this mean for SETBP1-HD:
While this review focuses on multiple genes and highlights a broader overlap between CAS and neurodevelopmental delay for monogenic disease, before this, the primary phenotype of CAS has been considered separate from the larger group of neurodevelopmental disorders, which may no longer be true thanks to this study. Individuals with SETBP1-HD can present with speech delay and intellectual disability (ID), autism spectrum disorder (ASD), or attention-deficit/hyperactivity disorder (ADHD). The work here may aid in future additional SETBP1-HD individuals being diagnosed due to the newly outlined phenotypic overlap. Additionally, SETBP1 loss of function variants were detected in all three cohorts in this review, highlighting a larger role for SETBP1 in speech and language development that can be investigated in future research, potentially providing direction for specific pathways or mechanisms to target. SETBP1 was 1/9 candidate genes exhibiting a high level of independent supporting evidence for this association. Despite these findings, speech genetics and future insights will remain limited by the need for more available population-based cohorts with high-quality genetic and phenotypic data. This emphasizes the important role of the SETBP1-HD community in engaging with researchers to continue to build these resources to aid future research.

Accessing the Review article:
The full review article titled “Genetic architecture of childhood speech disorder: a review” published in *Molecular Psychiatry* on February 16, 2024, can be accessed here: https://www.nature.com/articles/s41380-024-02409-8

Other related resources:
https://www.setbp1.org/setbp1-disorder-speech-language-paper-just-released/
Morgan et al. *European Journal of Human Genetics* 202: https://rdcu.be/cjud0

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